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Dendritic cell harmonised immunity to poultry pathogens; a review

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Dendritic cells (DCs) are antigen-presenting cells (APCs) with the unique ability to induce both innate immune responses and a highly specific acquired immunity. DCs are crucial to induce immunity, and their maturation and functions are influenced by microbial and environmental stimuli. Chicken DCs are composed of several subtypes including bursal secretory dendritic cells (BSDCs), follicular dendritic cells (FDCs), and thymic dendritic cells (TDCs). DC maturation depends on the nature of the perturbation and permits unique and efficient immune responses for each pathogen. DCs differentially recognise the viruses, bacteria, parasite and fungi and specifically regulate the immune response. Dendritic cells (DCs) are 'nature's adjuvants' and, as such represent an essential component of any vaccination strategy. The understanding of DC regulatory mechanisms opens a new horizon for the development of new vaccines and their targeting with the vaccination for elicitation of better immunity levels. The following review summarises the current state of knowledge of DCs and their specific functions during host pathogens interaction.

Keywords: dendritic cells; immunity; virus; bacteria; parasite; vaccines; poultry

Introduction

Poultry are raised surrounded by pathogens that include viruses, fungi, bacteria, and parasites, and other stress factors that can affect the performance and health of birds. To cope with these pathogens and unhealthy conditions, birds have a well-defined immune system. Innate immunity senses these pathogens by their specific molecular structure and passes pathogen-specific signals to adoptive immune system for the initiation of signal dependent immune responses. The adaptive immune system is comprised of entities such as B cells which produce specific antibodies, $CD4^+$ T cells for production of cytokines

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and immune regulation and $CD8^+$ T cells to kill antigen infected cells. The major focus for this review is on vital cells of the innate immune system of poultry, the dendritic cells.

Dendritic cells were discovered by Canadian scientists Ralph Steinman and Zanvil Cohn in 1973 (Steinman and Cohn, 1973), who were subsequently awarded the Noble Prize in 2011. The first article that reported the avian dendritic cells from caecal tonsils was published by Olah and Glick (1979) and subsequently, three major subsets of dendritic cell were identified in chicken lymphoid organs and epidermis (Igyártó *et al.*, 2006; Del Cacho *et al.*, 2009). Distinctive features of dendritic cells in immunity have now been reported after decades of scepticism. These are a diverse group of cells that are reknown for their antigen recognition roles. They are involved in other important immune functions like antigen presentation, initiation of adoptive immune responses, generation of immunological memory (Steinman, 1991).

Dendritic cells work as sentinels of the immune system and are present in every part of the body including skin, peripheral blood, mucosal surfaces, interstitial tissues, and in lymphoid and non-lymphoid tissue (Yasmin *et al.*, 2015; Rehman *et al.*, 2016). Dendritic cells recognise the pathogens by pattern recognition receptors including toll like receptors (TLR), cytoplasmic nucleotide-binding oligomerisation domain (NOD) like receptors, retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and C-type lectins, and initiate innate immune responses (Akira *et al.*, 2006). Pathogen activation causes many changes such as maturation, production of cytokines and the expression different co-stimulatory molecules (Banchereau and Steinman, 1998; Liu and Nussenzweig, 2010).

In last decade, much work has been done on dendritic cell biology, function, and immune responses in avian species. Extensive reviews on dendritic cell phenotype and ontogeny (Nagy *et al.*, 2016) and their regulation (De Geus and Vervelde, 2013) have been published. However, review articles about immunological functions in poultry are scarce.

Biology of dendritic cells

Dendritic cells are derived from bone marrow derived haematopoietic stem cells precursors expressing leukocyte antigen $CD45^+$. Diversified dendritic cells with specialised functions are formed through diverse ontogenic pathways, as reviewed by Merad *et al.* (2013). In a steady state these reside in blood and peripheral tissues. The phenotype of avian DCs is less understood because of a lack of specific markers but these can be cultured and activated by LPS. These activated DCs express CD11, C type lactin DEC205, activation marker of MHC II and CD40 (Wu *et al.*, 2010; De Geus *et al.*, 2012).

Immature dendritic cells work as immunological sensors and are activated directly by pathogens or other innate responses, signalling to the immune system to act against potentially harmful antigens (*Figure 1*) (Ueno *et al.*, 2007). Acquired immunological response is highly dependent on the signal of these cells. Dendritic cells are activated by different type of signals, such as direct capture of antigens, pathogen invasion, innate immune cells, dying cells and microenvironment (*Figure 1*). Immature DCs sense pathogen associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs), including toll-like receptors (TLRs) cell surface C-type lectin receptors (CLRs), and intracytoplasmic nucleotide oligomerisation domain (NOD)-like receptors (NLRs) (Ueno *et al.*, 2007; Liang *et al.*, 2015).

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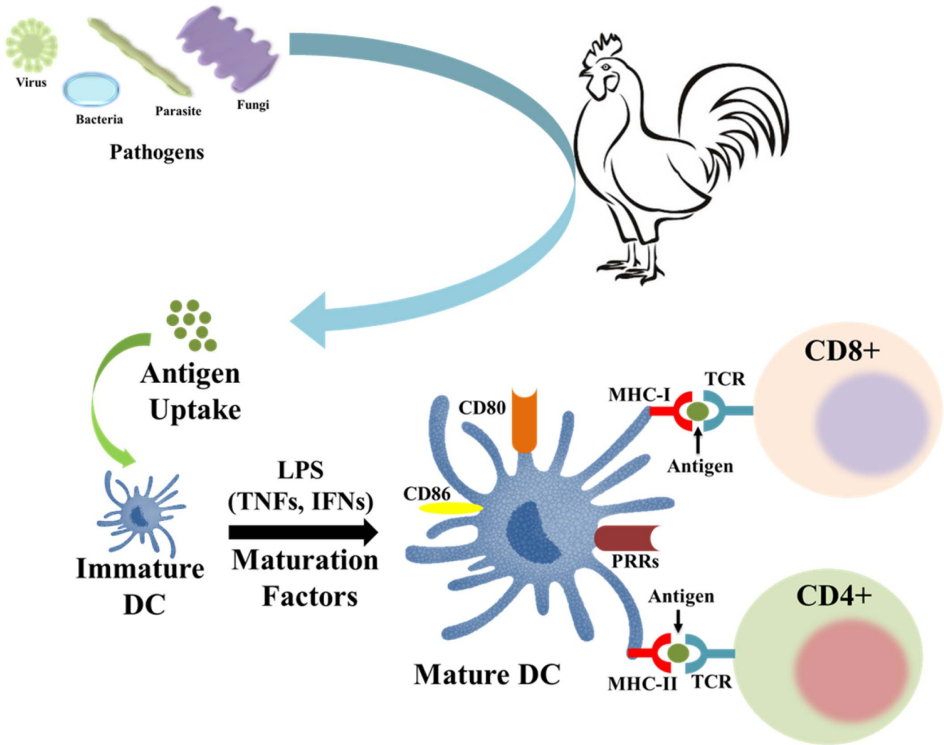


Figure 1 Dendritic cell maturation and activation of CD4+ and CD8+ T cells in response to pathogens. Schematic drawing depicting the differentiation of immature DC into mature DC by up-taking antigen. This process involved in morphological changes in mature DC as well as development of strong co-stimulatory molecules for the activation of T cells as well as pattern recognition sites on the surface of DC.

Adequate stimulation of the adaptive immune responses mainly depends on dendritic cell signals. Less scientific data is available about adaptive immune regulation in avian species compared to human and mice (Staines *et al.*, 2013). Activated DCs express high level of the MHC I and MHC II which are recognised by the CD8+ and CD4+ T cells respectively. These cells are present at the antigen entry sites, from where DCs recognise them, then migrate to lymphoid organs and leads to the stimulation of naïve T cells (Liang *et al.*, 2015). T cell maturation, in response of DCs signalling, is controlled by the microenvironment created by production of cytokine from DCs which direct activation toward Th1 or Th2 immune response immunity (Rissoan *et al.*, 1999).

DEC205 is a C-type lectin endocytic receptor of the mannose receptor family and is mostly known to involve antigen cross presentation (Cheong *et al.*, 2010), recognition of apoptotic cells (Shrimpton *et al.*, 2009) and enhances antigen presentation via MHC II +ve lysosomal compartments (Mahnke *et al.*, 2000). DEC205 was noted in spleen on the antigen trapping sites and thymus to educate T cells and also in bursa for diversification of B cells of chickens (Staines *et al.*, 2013).

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Antigen specific responses

RESPONSE TO VIRAL DISEASES

Dendritic cells have a undetermined role in viral infections, and viral interactions with dendritic cells have not been well understood in poultry (Yasmin *et al.*, 2015). Many viral components can activate and promote the production of cytokines. The ability of DCs to escalate the recruitment of T cells, production of antibodies from B cells and signalling to other innate immune cells may help in production of strong cell mediated immune response and viral clearance from the infected tissue. However, virus and dendritic cell interactions do not always support the host and these may affect the maturation and functioning of dendritic cells. Highly pathogenic avian influenza (HPAI) compared to low pathogenic avian influenza (LPAI), increases the expression of IL-8, IFN-α, IFN-γ mRNA, viral RNA and in TLR1, 3, and 21 mRNA of dendritic cells which may lead to deregulation of immune response (*Table 1*) (Vervelde *et al.*, 2013).

Similarly, (Kalaiyarasu *et al.*, 2016) found that monocyte derived DCs (chMoDCs) from chicken peripheral blood are the target of HPAI and cause the death of DCs, and this was greater for HPAI than LPAI. HPAI impair the activation of DCs and increase the expression of INFs and cytokines (IL-1β, IL-6, IL-18 and TNF-α factor) at the early phase of infection. However, (Rebel *et al.*, 2011) found that chickens infected with LPAI or HPAI express the same level of viral RNA, cytokine mRNA and same influxes of KUL01+ macrophages and DCs, but the location of the virus varies in the lungs. Previously, Waithman and Mintern (2012) reported that the AI virus infection of human myeloid DCs inhibits maturation and impairs cross presentation of antigens via MHC1. AI virus infection in chicken DCs decreases the level of glycan-recognising antibodies, when measured by glycan array analysis (*Table 1*) and there is an increasing trend in anti-glycan antibodies against specific glycan antigen which was observed by ELISA (De Geus *et al.*, 2013). Liang *et al.* (2015) compared the effect of vaccine strain of inactive infectious bursal disease virus (IBDV) with live IBDV, and found that inactive IBDV have stronger capability to up-regulate expression of CD40 and CD86 molecules and stimulate naive T cells proliferation than live IBDV. This may be due to impairment of dendritic cells by IBDV (Liang *et al.*, 2015). Infection of chBM-DCs with virulent live IBDV increases the expression of TLR3, Th1-like cytokines, IFN-γ and IL-12α, indicating they are the target of IBDV (Yasmin *et al.*, 2015; Rehman *et al.*, 2016). Response of DCs to other poultry viruses is not clear and further studies regarding this interaction with *e.g*. Newcastle disease (ND), infectious bronchitis, infectious laryngotracheitis remains to be explored.

RESPONSE TO BACTERIAL DISEASES

To protect the host, DCs are one of the most important cells to initiate innate and adoptive immune responses after encountering the bacterial pathogens and their products. DCs play a significant role in enhancing immune responses during bacterial infections. Stimulation of chi-BMDCs with *Bacillus subtilis* B10 (Bs), *Saccharomyces boulardii* (Sb), co-culture of Sb + Bs, lipopolysachride (LPS), and phosphate buffer saline (PBS) as a control group at three, six, and 12 hour intervals resulted in the change of phenotype and biological functions including engulfment, degradation and attachment of bacteria on the cells surface (*Table 1*). Treatment of chi-BMDCs with LPS or beneficial bacteria increased the expression of TLR1, TLR2, TLR4, chicken specific TLR15, MHC-II, CD40, CD80 and CD86 compared to a control. Furthermore, higher concentration of IL-1b, IL-4, IL-10, IL-17, TGF-β, and lower levels of INF-γ and IL-8 were observed in beneficial bacteria treated groups (Rajput *et al.*, 2014). Treatment with vaccine candidate, *S. enteritidis* and its serovar *Gallinarum* lead to phenotypical and functional maturations

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of chi-BMDCs as well as increased expression of IL-6 and IL-12 cytokines. These bacteria upregulated the expression of CD40, CD80, and MHC-II from Chi-BMDCs (*Table 1*) (Kamble *et al.*, 2016a; 2016b). Chicken BMDCs from Fayoumi and leghorn chickens exhibit different expression of immune genes in response to LPS stimulation, including higher MHC-11 surface expression, phagocytic ability and production of NO (Van Goor *et al.*, 2016).

The ideal result after bacterial engulfment from dendritic cells is the destruction of invading pathogen, and dendritic cells perform this efficiently (Rajput *et al.*, 2014; Kamble *et al.*, 2016a; 2016b).

Table 1 Role of different pathogens on dendritic cells by dysregulation in cytokines and their ultimate impaired function in maturation of dendritic cells and immune response.

Pathogen	Deregulatory cytokines	Impaired functions	Reference
Avian influenza virus	Not studied	Target humoral immune response by attachment and infection of chicken DC with AIV via glycan-binding receptors	(De Geus *et al.*, 2013)
Avian influenza virus	INF-α, IFN-β, IFN-γ, IL-1β, TNF-α, IL-18, TLR3, TLR7, TLR15 and TLR21	Suppress maturation of monocyte-derived DCs	(Kalaiyarasu *et al.*, 2016)
Avian influenza virus	IL-8, IFN-α, IFN-β, IFN-γ, TLR1, TLR3, and TLR21	Dysregulation of immune response by enhanced DCs activation	(Vervelde *et al.*, 2013)
Infectious bursal disease virus	expression profile of CD40 and CD86 molecules	Impaired DC maturation and functions, no specific immune response or undeveloped immune memory	(Liang *et al.*, 2015)
Very virulent live IBDV	TLR3, CCR7, IFN-γ and IL-12α	Impaired immunity by direct targeting bone-marrow derived DCs	(Yasmin *et al.*, 2015)
Newcastle disease virus	IFN-γ, IFN-β, TLR3	Impaired DC maturation and innate antiviral immunity	(Honda *et al.*, 2003)
Newcastle disease virus like particle	TLR4 and NF-κB pathway	Trigger maturation and migration of murine DC and impair innate immune response	(Qian *et al.*, 2017)
Bacillus subtilis B10	IL-1β, IL-17, IL-4, TGF-β, IL-10, IL-8 and INF-γ	Impair DC and immune functions by targeting TLR and other associated cytokines	(Rajput *et al.*, 2014)
Salmonella enteritidis ghost	IL-6 and IL-12p40, IL-2 and IFN-γ	Immature bone-marrow derived DCs.	(Kamble *et al.*, 2016a)
Salmonella enterica serovar Gallinarum	IL-6, IL-10 and IFN-γ	Invade bone-marrow DC and impair their maturation, and resist the induction of cellular immune response	(Kamble *et al.*, 2016b)
Toxoplasma gondii	MHC II and co-stimulatory molecules, CD40 and CD80	DC hide viable replicating *T. gondii* tachyzoites from the immune system	(Quéré *et al.*, 2013)
Eimeria tenella	TLR1A, TLR4, TLR5, TLR7 and TLR21, IFN-α, IFN-β, IFN-γ, IL-1β, and IL-12	Impair maturation of DC	(Hemmi and Akira, 2005, Zhang *et al.*, 2012)
Eimeria spp.	IL-2, IL-4, IL-16, IL-10, IFN-γ	Impaired immune response	(del Cacho *et al.*, 2012)
Eimeria tenella	IL-2-, IL-4-, IL-6-, and IFN-γ	Impair maturation of DC and poor immune response	(del Cacho *et al.*, 2016)

RESPONSE TO PARASITIC DISEASES

Parasites have the ability to alter DC function allowing them to evade from lethal immune responses (*Table 1*). *Toxoplasma gondii* tachyzoites are able to replicate in

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chicken splenic DCs without activating these cells, making them cellular carriers (Quéré *et al.*, 2013). Immunisation of chickens infected with *Eimeria tenella* with pulsed DCs or exosomes increased the numbers of cells expressing IL-2-,IL-16-, and IFN-γ, IgG and/or IgA. After *E. tenella* challenge, DCs pulsed or derived from exosome pulsed *E. tenella* immunised chickens, exhibited reduced oocyte shedding, lower mortality, better body weight gain and FCR compared to birds which were given antigen alone (Del Cacho *et al.*, 2011). These researchers described that *E. tenella, maxima* and *acervulina* loaded exosomes of DCs could boost the cellular secretions of IL-16 and the Th1cytokines, IL-2 and IFN-γ, increase antigen stimulated proliferative responses, and higher numbers of IgG and IgA-producing cells compared to non-immunised and infected birds (del Cacho *et al.*, 2012). Similar results were found when the chickens were vaccinated with serum exosomes containing parasite antigens (del Cacho *et al.*, 2016). It has been reported in mouse models that temporary depletion of DCs increased mortality during *Toxoplasma gondii* infection (Liu *et al.*, 2006; Yao *et al.*, 2009). This field needs more attention to completely understand pathogenesis, designing effective vaccines and control of parasitic diseases of poultry.

RESPONSE TO FUNGAL INFECTIONS

Mycotoxins are one of the major cause of immunosuppression in poultry, leading to other bacterial and viral infections (Dhama *et al.*, 2013). Most common fungal diseases of poultry are aspergillosis and candidiasis. Mycotoxicosis is often caused by the aflatoxins, ochratoxins, trichothecene fusariotoxins and fusariotoxins and C-type lectins (Neumann and Jacobson, 2010), TLR2, TLR3, TLR4, TLR7, TLR9, mannose receptors and NOD-like receptors are involved in sensing fungi and its metabolites (Roy and Klein, 2012). Aflatoxin B1 increases the secretion of IL-1b and IL-6 from human CD11c+ DCs (Mohammadi *et al.*, 2014). Aflatoxins upregulate the expression of CD25 and CD80/86, enhance antigen presenting capacity but have no effect on the phagocytic activity of porcine DCs (Mehrzad *et al.*, 2015). However, aflatoxin B1 dysregulate the antigen presenting capacity of porcine DCs (Mehrzad *et al.*, 2014). Similarly, deoxynivalenol (DON) and T-2 affect the function and maturation of DCs (Bimczok *et al.*, 2007; Escrivá *et al.*, 2015). Activated DCs present fungal peptides to T cells, and activated CD4 and CD8 cells produce IFN which stimulates macrophages, which kill fungus and fungus infected cells. Fungally infected macrophages are killed by the activated CD8 T cells. Experimental infection studies regarding the interaction between DCs and fungi and their toxins in poultry are limited and there is a need for studies to fully elucidate the pathogenesis and possible intervention strategies.

Exploitation of dendritic cells

The poultry industry mainly relies on the vaccination for the prevention and control of a wide range of pathogens (Marangon *et al.*, 2007). A more detailed understanding of antigen presentation mechanisms is needed to improve the vaccines (Mattsson *et al.*, 2011; Wu and Kaiser, 2011) and DCs are one of the most important cells involved in antigen presentation and immune regulation (Banchereau and Steinman, 1998). Recent developments in the evaluation of DC biology and immune interactions revealed the possibilities for their use as immune modulators and adjuvants in vaccination. DCs can be exploited in two ways for the development of effective vaccines; one by their *in vivo* targeting and secondly by the generation of antigen loaded DCs (Ueno *et al.*, 2007).

Dendritic cells have been evaluated in the vaccination of ND, IBD, salmonellosis, and coccidiosis. Jiang *et al.* (2015) compared the efficacy of ND vaccine by synthesising

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recombinant *Lactobacillus plantarum* expressing haemaglutinin–neuraminidase protein alone or fused along with DC targeting peptides. Results showed that the vaccine plus DC peptides significantly improved the Ig A and CD3+CD4+ T cells in the spleen and peripheral blood leukocytes. Inactive IBDV strongly upregulated DC surface expression of CD40 and CD86, while live IBDV did not have this ability (Liang *et al.*, 2015; Rehman *et al.*, 2016) indicating the possibilities of DCs to increase the efficacy of IBDV vaccines. Salmonella vaccines interact with the chBM-DCs by activation, maturation and cytokine production which demonstrates the potential of antigen delivery *via* dendritic cells (Kamble *et al.*, 2016a; 2016b).

Immunisation with *E. tenella* loaded DCs and *E. tenella* pulsed DCs derived exosomes efficiently protected the chicken challenged with *E. tenella* after 10 days of immunisation and reduced oocyte shedding, increased body weight gain and improved FCR and mortality in a chicken challenge model (del Cacho *et al.*, 2012). Similar results of protection against *E. tenella, maxima, and acervulina* challenge were observed by vaccinating the chicken with *Emeria* pulsed DCs derived exosomes (Del Cacho *et al.*, 2011). These authors observed an increase resistance in chickens against *E. tenella* infection after immunisation with antigen loaded caecal tonsil DC exosomes (del Cacho *et al.*, 2013). Fungal pulsed and RNA transfected DCs have been proven to enhance the activation of CD4+ cells, resistance to infection and decrease the toxin load in different tissues of mice (Bacci *et al.*, 2002; Bozza *et al.*, 2003; 2004). However, dendritic cell targeted or loaded fungal vaccines remains to be explored for poultry.

DC surface receptor targeted vaccines can be generated by attaching DCs specific ligands with the antigens (Apostolopoulos *et al.*, 2013). It is well known that DCs can be targeted by activating TLR ligands which then show more potent immune response. Chemokine receptor targeting in DCs induces enhanced immune response both *in vivo* and *in vitro*. DC targeting studies show an increase in production of proinflammatory vaccines and promising results when these were targeted by poly lactide-co-glycolic acid nanoparticles base tumour vaccine, which silence the immunosuppressive gene of DCs (Heo *et al.*, 2014). Nanoparticle based targeting of DCs is an emerging trend for the development of more immune enhancer vaccines.

Chicken BM-DCs can be targeted by using CpG oligonucleotides which stimulate the maturation and expression of CD40 and CD 86 molecules (Fu *et al.*, 2014). Oxidation of DCs can be prevented by bursopentine (Qin *et al.*, 2015) which may be helpful in certain disease conditions. However, different methods and strategies for the production of clinically effective DCs based or targeted vaccines need to be developed in future.

Conclusions

DCs provide an essential link between the innate and adaptive immune responses. In recent years, with the emergence of new chicken DCs markers, it has become increasingly possible to culture chicken DCs *in vitro*. DCs are an attractive target for therapeutic manipulation of the immune system and to enhance insufficient immune responses against infectious diseases. Vaccination strategies involving DCs have become useful owing to the special properties of these cells in coordinating innate and adaptive immune responses. Insights into the roles of DCs in host antiviral defence may supply useful information for the development of novel preventive or therapeutic strategies against viral infections in poultry.

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